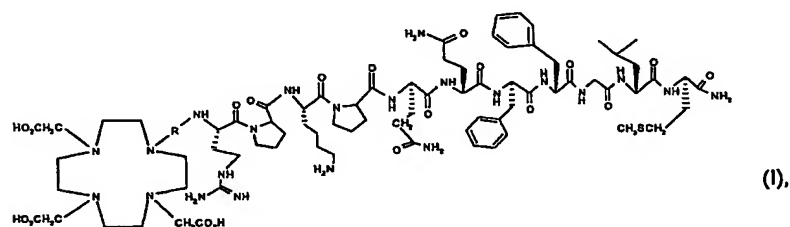


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Claims:

1. Use of radio-nuclide labelled conjugates of substance P and a chelator molecule, having the abbreviation

Chelator-R-Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>-Gln<sup>6</sup>-Phe<sup>7</sup>-Phe<sup>8</sup>-Gly<sup>9</sup>-Leu<sup>10</sup>-Met<sup>11</sup>-NH<sub>2</sub> and comprising compounds of formula I

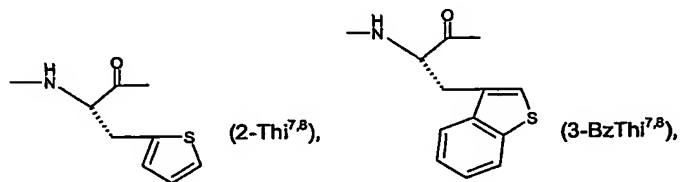


wherein

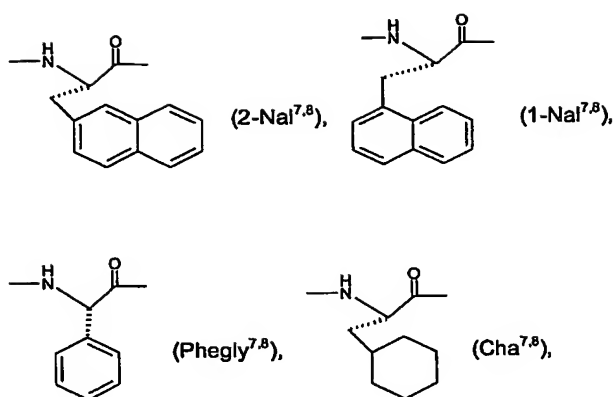
R is -CH<sub>2</sub>-C(O)-, -C(CO<sub>2</sub>H)CH<sub>2</sub>CH<sub>2</sub>-C(O)- or -C(CO<sub>2</sub>H)CH<sub>2</sub>-C(O)-,

or an analogue of formula I with at least one of the subsequent modifications in the amino acid sequence of substance P:

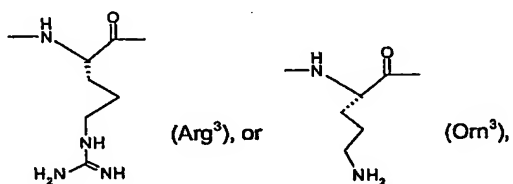
- a) replacement of Met<sup>11</sup> by -NH-CH(CH<sub>2</sub>CH<sub>2</sub>-SO<sub>2</sub>-CH<sub>3</sub>)-C(O)- (Met(O<sub>2</sub>)<sup>11</sup>), -NH-CH(CH<sub>2</sub>CH<sub>2</sub>-SO-CH<sub>3</sub>)-C(O)- (Met(O)<sup>11</sup>), or -NH-CH[CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>]-C(O)- (Ile<sup>11</sup>),
- b) replacement of Leu<sup>10</sup> by -NH-CH[CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>]-C(O)- (Ile<sup>10</sup>),
- c) replacement of Gly<sup>9</sup> by -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)- (Sar<sup>9</sup>),
- d) replacement of Phe<sup>7</sup> or Phe<sup>8</sup> or both Phe<sup>7</sup> and Phe<sup>8</sup> by residue of formulae



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e) replacement of Lys<sup>3</sup> by residue of formulae



f) truncation of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>, or

g) replacement of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup> by -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)- (Sar),

and wherein the conjugate is labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dysprosium 162, Dysprosium 165, Dysprosium 167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149,

as active ingredient in radiopharmaceutical or radio-diagnostic formulations for targeting or treating brain tumors, especially gliomas.

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2. Use according to claim 1, wherein the amino acid sequence in formula I corresponds to formulae

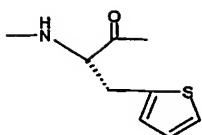
- a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub>,
- b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- c) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met-NH<sub>2</sub>,
- d) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met-NH<sub>2</sub>,
- e) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met-NH<sub>2</sub>,
- f) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- g) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- h) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- i) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- j) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Sar-Leu-Met-NH<sub>2</sub>,
- k) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- l) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Sar-Leu-Met-NH<sub>2</sub>,
- m) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- n) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met-NH<sub>2</sub>,
- o) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>.

3. Use according to claim 1, wherein the compounds of formula I comprise in the 11-position of the natural substance P sequence a methioninsulfone residue of formula -NH-CH(CH<sub>2</sub>CH<sub>2</sub>-SO<sub>2</sub>-CH<sub>3</sub>)-C(O)- instead of a methionin residue.

4. Use according to claim 1, wherein the glycine residue in position 9 of the natural substance P sequence is replaced by a sarcosine residue of formula -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)-.

5. Use according to claim 1, wherein the phenylalanine residue in the 7- or 8-position or in both said positions of the natural substance P sequence is replaced by a 3-(2-thienyl)-alanine residue of formula

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6. Use according to claim 1, wherein the phenylalanine residue in the 8-position of the natural substance P sequence is replaced by a 3-(2-thienyl)-alanine and the glycine residue in position 9 is replaced by a sarcosine residue.

7. Use according to claim 1, wherein the methionine residue in the 11-position of the natural substance P sequence is replaced by a methioninsulfone residue, and the phenylalanine residue in the 8-position of the natural substance P sequence is replaced by a 3-(2-thienyl)-alanine residue, or the glycine residue in position 9 is replaced by a sarcosine residue.

8. Use according to claim 1, wherein the amino acid sequence in formula I corresponds to formulae

- a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met-NH<sub>2</sub>,
- c) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met-NH<sub>2</sub>,
- d) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Phe-Gly-Leu-Met-NH<sub>2</sub>,
- e) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- f) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>,
- g) Arg-Pro-Lys-Pro-Gln-Gln-Thi-Thi-Gly-Leu-Met-NH<sub>2</sub>, or
- h) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>.

9. Use according to claim 1, wherein the amino acid sequence in formula I corresponds to formulae

- a) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Sar-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>, or
- b) Arg-Pro-Lys-Pro-Gln-Gln-Phe-Thi-Gly-Leu-Met(O<sub>2</sub>)-NH<sub>2</sub>.

10. A method of targeting brain tumors, localizing or treating brain tumors and the satellite lesions thereof in a host afflicted with brain tumors, e.g. gliomas, in administering to the host at least one compound of formula I or an analogue of a compound of formula I.

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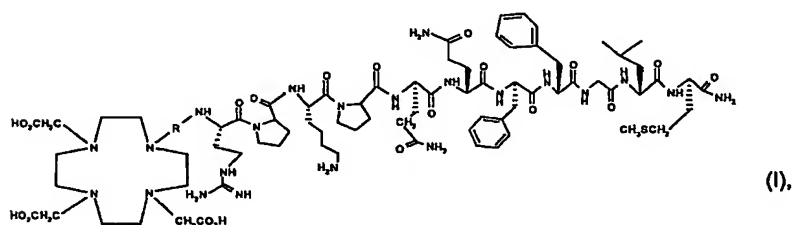
11. A therapeutic or diagnostic method for targeting brain tumors, localizing or treating brain tumors and the satellite lesions thereof in a mammal comprising administering to a mammal in need of such therapy, an effective amount of a radio-nuclide labelled substance P conjugate of formula I or an analogue thereof.

12. A method of delivering a radio-nuclide labelled substance P conjugate of formula I or an analogue thereof to a host, comprising administering to a host a radio-nuclide labelled substance P conjugate of formula I or an analogue thereof.

13. Use of a radio-nuclide labelled substance P conjugate of formula I or an analogue thereof for the manufacture of a medicament useful for the detection and therapeutic treatment of brain tumors and satellite lesions thereof in a mammal, such as a human.

14. A radio-nuclide labelled substance P conjugate of formula I or an analogue thereof for use in medical therapy.

15. Conjugates of substance P analogues and a chelator molecule, whereby substance P conjugate has the abbreviation Chelator-R-Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>-Gln<sup>6</sup>-Phe<sup>7</sup>-Phe<sup>8</sup>-Gly<sup>9</sup>-Leu<sup>10</sup>-Met<sup>11</sup>-NH<sub>2</sub> and comprises compounds of formula I



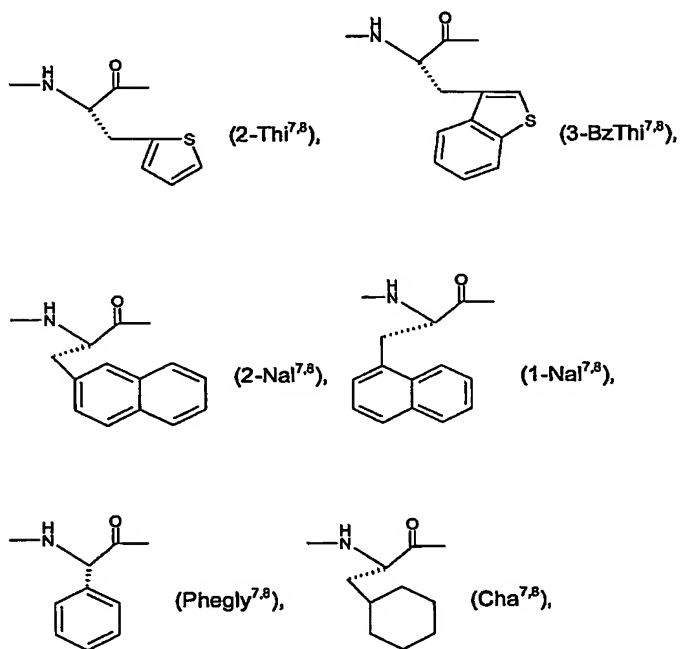
wherein

R is -CH<sub>2</sub>-C(O)-, -C(CO<sub>2</sub>H)CH<sub>2</sub>CH<sub>2</sub>-C(O)- or -C(CO<sub>2</sub>H)CH<sub>2</sub>-C(O)-, with the proviso that R is -CH<sub>2</sub>-C(O)-, when the conjugate comprises the substance P sequence,

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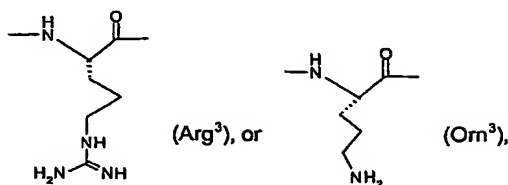
and an analogue of formula I with at least one of the subsequent modifications in the amino acid sequence of substance P:

- a) replacement of Met<sup>11</sup> by -NH-CH(CH<sub>2</sub>CH<sub>2</sub>-SO<sub>2</sub>-CH<sub>3</sub>)-C(O)- (Met(O<sub>2</sub>)<sup>11</sup>), -NH-CH(CH<sub>2</sub>CH<sub>2</sub>-SO-CH<sub>3</sub>)-C(O)- (Met(O)<sup>11</sup>), or -NH-CH[CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>]-C(O)- (Ile<sup>11</sup>),
- b) replacement of Leu<sup>10</sup> by -NH-CH[CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>]-C(O)- (Ile<sup>10</sup>),
- c) replacement of Gly<sup>9</sup> by -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)- (Sar<sup>9</sup>),
- d) replacement of Phe<sup>7</sup> or Phe<sup>8</sup> or both Phe<sup>7</sup> and Phe<sup>8</sup> by residue of formulae



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e) replacement of Lys<sup>3</sup> by residue of formulae

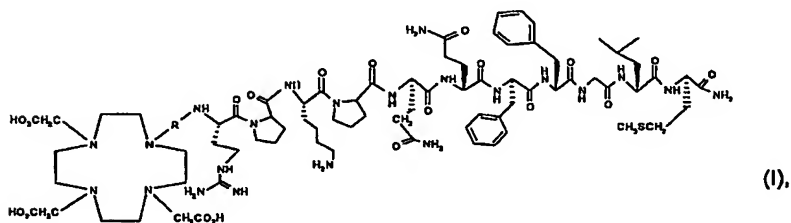


f) truncation of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>, or

g) replacement of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup> by -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)- (Sar),

and wherein the conjugates are unlabelled or labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dysprosium 162, Dysprosium 165, Dysprosium 167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149.

16. A composition comprising (a) at least one pharmaceutical carrier and (b) at least one conjugate of substance P or an analogue of substance P and a chelator molecule, whereby substance P conjugate has the abbreviation Chelator-R-Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>-Gln<sup>6</sup>-Phe<sup>7</sup>-Phe<sup>8</sup>-Gly<sup>9</sup>-Leu<sup>10</sup>-Met<sup>11</sup>-NH<sub>2</sub> and comprises compounds of formula I

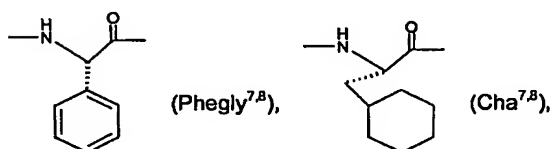
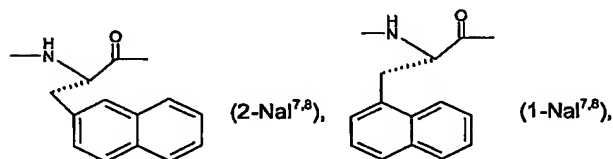
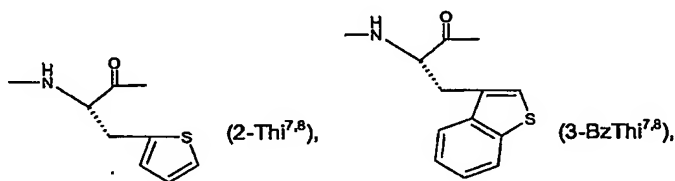


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wherein

R is  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-\text{C}(\text{CO}_2\text{H})\text{CH}_2\text{CH}_2-\text{C}(\text{O})-$  or  $-\text{C}(\text{CO}_2\text{H})\text{CH}_2-\text{C}(\text{O})-$ , with the proviso that R is  $-\text{CH}_2-\text{C}(\text{O})-$ , when the conjugate comprises the substance P sequence, and an analogue of formula I with at least one of the subsequent modifications in the amino acid sequence of substance P:

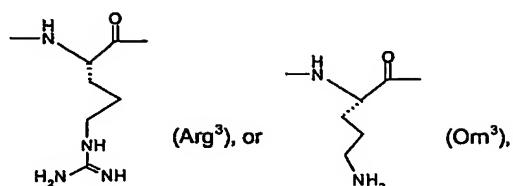
- replacement of Met<sup>11</sup> by  $-\text{NH}-\text{CH}(\text{CH}_2\text{CH}_2-\text{SO}_2-\text{CH}_3)-\text{C}(\text{O})-$  (Met(O<sub>2</sub>)<sup>11</sup>),  $-\text{NH}-\text{CH}(\text{CH}_2\text{CH}_2-\text{SO}-\text{CH}_3)-\text{C}(\text{O})-$  (Met(O)<sup>11</sup>), or  $-\text{NH}-\text{CH}[\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3]-\text{C}(\text{O})-$  (Ile<sup>11</sup>),
- replacement of Leu<sup>10</sup> by  $-\text{NH}-\text{CH}[\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3]-\text{C}(\text{O})-$  (Ile<sup>10</sup>),
- replacement of Gly<sup>9</sup> by  $-\text{N}(\text{CH}_3)-\text{CH}_2-\text{C}(\text{O})-$  (Sar<sup>9</sup>),
- replacement of Phe<sup>7</sup> or Phe<sup>8</sup> or both Phe<sup>7</sup> and Phe<sup>8</sup> by residue of formulae





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e) replacement of Lys<sup>3</sup> by residue of formulae



f) truncation of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup>, or

g) replacement of 1 to 5 amino acids of the sequence Arg<sup>1</sup>-Pro<sup>2</sup>-Lys<sup>3</sup>-Pro<sup>4</sup>-Gln<sup>5</sup> by -N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)- (Sar),

and wherein the conjugates are labelled with a radio-nuclide selected from the group consisting of Actinium-225, Bismut-212, Bismut-213, Lead-203, Copper-64, Copper-67, Gallium-66, Gallium-67, Gallium-68, Lutetium-177, Indium-111, Indium-113, Yttrium-86 and Yttrium-90, Dysprosium-162, Dysprosium-165, Dysprosium-167, Holmium-166, Praseodymium-142, Praseodymium-143, Promethium-149, and Terbium-149.